Annals of Nutritional Disorders & Therapy

Austin Publishing Group

Open Access Full Text Article

Review Article

Obesity: A Brief Approach to this New Pandemia

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Received: August 02, 2014; **Accepted:** September 16, 2014; **Published:** September 16, 2014

Abstract

Obesity is a condition in which excess body fat has accumulated to the extent that it has an adverse effect on physical, mental and/or social health. The global prevalence of obesity increased substantially in the past four decades regardless of age, gender, race, and ethnicity. Unlike other pandemics, obesity does not cause disease directly but instead functions as a potent independent risk factor for a number of pathologies, including type-2 diabetes, coronary artery disease, neurodegenerative disorders, and cancer, inducing immense harm in both health and economic terms. These pathologies are associated with the metabolic changes observed in the obesity, such as insulin resistance, and the inflammation and the evoked oxidative stress seem to be to a great extent the pathogenic elements. Human adipose tissue is a dynamic organ that profoundly contributes to the regulation of several (patho-) physiological processes, including embryonic development, systemic endocrine/metabolic homeostasis, immunomodulation, and it has been recognized as an organ with endocrine properties. Since a high number of non-pharmacological interventions are discussed, pharmacological interventions are not within the scope of this review. This review focuses comprehensively on obesity causes, consequences, and the role in obesity-related metabolic disorders of several adipokines.

Keywords: Obesity; White adipose tissue; Brown adipose tissue; Adipokines; Inflammatory signaling

Introduction

Obesity is a pathological condition in which excess body fat has accumulated to the extent that it has an adverse effect on a person's physical, mental and/or social health. The Obesity Society has taken the position that obesity be considered a disease because this fact will benefit the society in many ways: this will increase the funding resources for prevention, treatment and research, will encourage healthcare professionals to view treating obesity as a vocation worthy of effort and respect, and will reduce the stigma and discrimination experienced by many persons with obesity [1,2]. The global prevalence of obesity increased substantially in the past four decades regardless of age, gender, race, and ethnicity. According to the World Health Organization, in 2008, 1.5 billion adults were overweight, and of these over 200 million men and nearly 300 million women were obese [3]. The USA has not escaped this epidemic, with the incidence of obesity increasing from 13 % in the 1960s to over 35.5 % [4], and it is estimated that 164 million Americans will be obese by 2030 [5]. In Spain, recently, the prevalence of obesity is reaching alarming figures, exceeding 35% of the children. Unlike other pandemics, however, obesity does not cause disease directly but instead functions as a potent independent risk factor for a number of chronic pathologies, including type-2 diabetes, coronary artery disease, neurodegenerative disorders, and cancer [6], wreaking immense harm in both health and economic terms.

The most noticeably effect of obesity is an increase in fat mass, resulting from a longterm imbalance between energy intake and energy expenditure [7]. Evidences in the scientific literature suggest that the energy balance does not fit very well when analyzing the causes of the current obesity epidemic and, although genetics are able to explain up to 30% of the propability to become obese in infancy, it has been suggested that genetics might be influenced by many other factors including sedentarism and physical activity [8].

Obesity often leads to chronic activation of inflammatory pathways that are important in the pathogenesis of several metabolic changes observed in this new pandemia, such as insulin resistance, which is the consequence of adipose tissue inflammation [9].

Adipose tissue can be divided into 2 main types: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT represents the vast majority of adipose tissue in the organism and is the site of energy storage, having a key role in triglycerides storage during energy consumption and fatty acid release over periods of starvation [10,11]. The main role of BAT is nonshivering thermogenesis, particularly in small mammals and human neonates.

WAT is an important secretory organ which produces a number of molecules that putatively play critical roles in fuel homeostasis and contribute to maintain metabolic control. These bioactive molecules, generally termed 'adipokines', include leptin, adiponectin, TNF-α, IL-6, omentin, visfatin and apelin, among others. In fact, the number of adipokines has enlarged considerably during the last few years and nowadays more than 50 have been identified [12]. These adipokines are involved in the physiological regulation of fat storage, adipogenesis, energy metabolism, food intake and also play an important role in metabolic disorders. Adipokines may exert their physiological functions in WAT locally (autocrine/paracrine) and systemically (endocrine) and, in addition, WAT also expresses a high number of important receptors leading to the interaction between different organs and tissues involved in energy homeostasis, such as central nervous system, liver, skeletal muscle and pancreas [13].

Citation: Díaz-Castro J, Hijano S, Pulido-Morán M, Kajarabille N, Ochoa JJ. Obesity: A Brief Approach to this New Pandemia. Ann Nutr Disord & Ther. 2014;1(2): 1010.

The purpose of this review is to describe the obesity, its consequences, adipokines circulating during the obesity and their role in obesity-related metabolic disorders.

Definition of Obesity

Obesity is a chronic disease with a multifactorial origin, developed from the interaction of social, behavioral, psychological, metabolic, cellular, and molecular factors [14]. It is a serious problem which heightens the risk of several chronic illnesses and a condition under which adipose tissue is expanded and can be also defined as an increase in body weight resulting from an excessive fat accumulation.

The obesity epidemic, which started in the industrialized world, has progressed to become a worldwide pandemic in which the number of obese individuals worldwide now exceeds those who are malnourished [15].

The most widely used method of measuring and identifying obesity is the body mass index (BMI), a term originally coined by Ancel Keys (1972) [16]. The BMI cutpoints for adults that are endorsed by the World Health Organization (WHO) and government and research agencies in Canada are that overweight (sometimes called pre-obesity) be based on a BMI of 25-29.9 kg/m^2 and obesity a BMI of > 30 kg/m^2. Obesity can further be divided into class I (30-34.9 kg/m^2), class II (35.0-39.9 kg/m^2) and class III (40 kg/m^2) categories [17,18]. These BMI cutpoints reflect the increasing health risk of excess weight as BMI increases above the healthy weight range of 18.5-24.9 kg/m^2 [19] and, in this sense, the WHO defines obesity as a body mass index (BMI) > 30 kg/m^2 and defines overweight as with a BMI of 25 kg/m^2 [19].

As mentioned above, the global prevalence of obesity increased substantially in the past four decades regardless of age, gender, race, and ethnicity. In 2008, 1.5 billion adults were overweight, and of these over 200 million men and nearly 300 million women were obese [3].

Obesity increases mortality and the prevalence of several pathologies such as diabetes, cardiovascular diseases, and colorectal cancer, between many other metabolic disorders. Many reports in the scientific literature has emerged and they show that overweight and obesity have key roles in co-morbidities, which can lead to further morbidity and mortality [20]. The related health-care costs are also substantial. Therefore, it is of great importance to develop a public health approach to for the prevention of excess weight gain. However, public health intervention programs have had scarce success limiting the prevalence of obesity [21].

Causes of Obesity

Traditionally, obesity has been viewed as the result of an imbalance between energy intake and expenditure, driven by increased consumption of food with high caloric content and a sedentary lifestyle. Interindividual differences have been often ascribed to genetic variations in genes related to energy metabolism. In children, increased consumption of fats and carbohydrates and scarce physical activity have been linked with obesity [19], and many genetic and epidemiological studies in the 1980s on cohorts of twins and adopted children revealed a statistically significant contribution of genetics to the development of obesity [21,22,23].

The basic hypothesis of the cause of the disease is the existence of the "thirsty gene theory", which suggests that some specific populations may have genes that determine increased fat storage, fact that would provide a survival advantage during periods of starvation, however under current circumstances, increased storage of fat results in obesity and type-2 diabetes mellitus (DM) [19,21].

In recent years obesity and its related complications have also been associated with other factors such as endocrine disease, sleep, gut flora, or nutrients, which might increase susceptibility to weight-gain and obesity-related complications through epigenetic changes [20,24,25,26]. Recent progress in dissecting transcriptional alterations in gene networks, that are specifically linked to adipose tissue inflammation in obesity, highlight the importance of a tight coordination of such networks for appropriate gene expression for a healthy state. These alterations include activation and promoter binding of specific transcription factors, referred to as genomic regulators, the recruitment of chromatin modifying co-regulators, and the induction of non-coding RNAs referred to as epigenomic regulators [20].

Consecuences of Obesity

Evoked oxidative stress

Reactive oxygen species (ROS) are produced under physiological conditions in many pathologies, and they are the cause of direct or indirect damage in cell biomolecules; therefore, oxidative stress (OS) is involved in pathological processes such as obesity, diabetes, cardiovascular disease, and atherogenic processes. In this sense, obesity may induce systemic OS and this situation is associated with an impaired production of adipokines, contributing to the development of the metabolic syndrome [27]. The sensitivity of C reactive protein and other biomarkers of oxidative damage are higher in individuals with obesity and they are directly correlated with BMI, body fat, LDL oxidation, and triglyceride levels [28]; in contrast, antioxidant defense enzimes are negatively correlated with the amount of body fat [29,30]. A diet rich in fat and carbohydrates increases OS and inflammation in obese individuals [31,21].

Evidence of oxidative stress induced by obesity has been demonstrated by increased levels of lipid peroxidation markers, as well as reduced antioxidants such as glutathione (GSH) levels and superoxide dismutase and glutathione peroxidase enzymes. The mechanism underlying oxidative stress in obesity is multifactorial, including hyperglycemia, increased oxygen consumption, and cell

respiration rate; increased tissue levels of lipids and free fatty acids, inadequate antioxidant defense system, and chronic inflammation [32]. It is noteworthy the link between inflammatory signaling and oxidative stress, and in this sense, it has been reported that after M1 type macrophages infiltrate into the adipose tissue, they secrete more proinflammatory cytokines and produce ROS, which can recruit more macrophages and amplify the inflammatory response [33]. The obesity-related oxidative stress and inflammation have been also associated with insulin resistance.

The link between obesity and oxidative stress is also featured in the hepatic damage. Fatty acid accumulation stimulates ROS generation in the liver presumably due to enhanced β-oxidation and to the consequent electron overflow in the mitochondrial electron transfer

chain. [34]. However, a decrease in mitochondrial quinone pool and a related inhibition of mitochondrial oxidative metabolism were also suggested to underlie the increased mitochondrial ROS production in high fat diet [35]. Increased expression [36] and activity [37,38] of cytochrome P450 2E1 (CYP2E1) monooxygenase likely contributes to the oxidative stress, with a positive correlation between CYP2E1 and BMI [39].

Inflammatory signaling

Obesity often leads to chronic activation of inflammatory signaling which plays a major role in the pathogenesis of insulin resistance and other metabolic disorders. Most of the adverse metabolic changes associated with insulin resistance occur as a result of an inflammation of the adipose tissue. Therefore, obesity-induced inflammation and insulin resistance can be considered a key pathogenic link between immunology and metabolism, which some authors call "immunometabolism".

Current evidence demonstrates that activation and infiltration of immune cells, contributes to the inflammatory processes that takes place in adipose tissue. Immediately after activation, immune cells uptake and utilize high amounts of glucose, altering metabolic pathways that prevent glucose uptake and storage, in an adaptatory mechanism to provide immune cells with greater nutrient access [9]. This cross regulation linking metabolism and immunity suggest a new potential mechanism by which inflammation and insulin resistance can be studied.

Como se ha comentado, WAT represents the vast majority of adipose tissue in the organism and is the site of energy storage, whereas BAT participates in nonshivering thermogenesis. It is likely that adipose tissue is involved in the development of obesity-related disorders. WAT has a key role in triglycerides storage during energy consumption and fatty acid release over periods of starvation [10,11]. Further research has revealed that WAT is not an inert organ but rather a dynamic endocrine tissue that secretes adipokines to coordinate changes in nutrient intake, utilization, and storage [40]. Importantly, this active coordination of organism-wide metabolism is mediated not only by canonical neuroendocrine control but also by leukocytes that traffic to and reside in metabolic tissues [41].

In obese subjects, expansion of adipose tissue causes hypoxia, necrosis and stress, leading to necrosis of adipocytes. More than 90% of macrophages in WAT are localized in dead/necrotic adipocytes. The "Crown-Like Structure" [42] describes necrotic cells and lipid droplets [43] and the surrounding macrophages acting as scavengers of cell debris and lipid in the dead cells. Tow types of of macrophages has been identified in WAT: proinflammatory M1 type and anti-inflammatory M2 type [44].

Therefore, WAT is an important secretory organ which produces a number of molecules that putatively play critical roles in fuel homeostasis and contribute to maintain metabolic control. These bioactive molecules are generally termed 'adipokines' and include more than 50 [12].

Pathologies correlated with obesity

Obesity is a serious problem which heightens the risk of several chronic illnesses and a condition under which adipose tissue is increased and can be defined as an increase in body weight that results in excessive fat accumulation.

Cardiovascular risk

Multiple disease mechanisms link obesity with cardiovascular disease (CVD). Excess adipose tissue, specifically visceral fat, is associated with altered release of adipokines and chemical mediators [45,46]. Together, these mediators promote a proinflammatory and prothrombotic state contributing to CVD. Moreover, obesity increases the prevalence of CVD through risk factors associated with metabolic syndrome such as diabetes mellitus (DM), insulin resistance, hypertension, and dyslipidemia [47].

Other mechanisms linking obesity and CVD include neurohormonal activation with increased sympathetic tone, endothelial dysfunction, insulin resistance, obstructive sleep apnea, and turnover of free fatty acids (FA). However, it is still unclear if these mechanisms are independent of one another or if they all form part of a unified response by the organism. Obesity could influence atherosclerotic formation through the chronic state of hyperleptinemia and/or resistance to leptin in obese individuals. In vitro, studies have shown that leptin induces CRP expression, and increases oxidative stress in vascular endothelial cells, which contributes to the development of atherosclerosis [48-50].

Adiponectin is inversely associated with CVD [51]. The cardioprotective role of adiponectin at the endothelial level is exerted through multiple pathways, including suppressing the proliferation and migration of vascular smooth muscle cells [52], preventing neointimal formation in the vascular endothelium, and promoting tolerance in macrophages against proinflammatory cytokines [53]. Furthermore, adiponectin can also prevent atherosclerosis by increasing cholesterol efflux from macrophages [54], and lowering the expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1, interleukin-8, and E-selectin [55]. Finally, adiponectin also increases the expression of tissue inhibitor of metalloproteinase 1 in the muscle vasculature, which plays a key role in plaque stability [48,56].

Diabetes mellitus (DM) type-2

Obesity often leads to activation of pro-inflammatory pathways that are important in the pathogenesis of insulin resistance as it will be commented along this review. The adverse metabolic changes associated with insulin resistance occur as a result of the inflamed adipose tissue and the pro-inflammatory adipokines produced which act as key active participants. Inflammatory mediators activate enzyme complexes that promote phosphorylation of serine residues in the insulin receptor substrate-1 instead of tyrosine residues and inhibit insulin signaling cascade [57]. Resistin is implicated in the regulation of inflammation, artherosclerosis and their levels have been increased in human obesity and DM type-2, and its effects are antagonized by adiponectin [58]. Retinol Binding protein 4 (RBP-4) is increased in human obesity and type-2 DM. In this sense, a positive relationship was found between RBP-4 and insulin-resistance severity in obese, glucose-intolerant, type-2 diabetics and nonobese subjects with a strong family background for type-2 DM [59-61]. Omentin-1 has been linked to obesity, type-2 DM and metabolic syndrome [62,63].

Cancer

It has been estimated that about 20% of all cancers are caused

by excess weight [64], and the Million Women Study, the largest study of its kind on women, has shown that approximately half can be attributed to obesity in postmenopausal women [65]. There are many prospective epidemiological studies which have demonstrated a direct association between overweight and cancer, even though obesity alone does not apparently heighten cancer risk in all tissues by the same amount [64-69], current evidence suggest that overweight and increased body fat mass increase the incidence and prevalence from diverse types of cancers, including colon, breast (in postmenopausal women), endometrium, kidney (renal cell), esophagus (adenocarcinoma), stomach, pancreas, gallbladder and liver, among others [67].

In the obese, the mechanisms which may foster or promote cancer occurrence or progression are usually classified as being of two types. They may be universal and direct in nature in that they apply to all or the majority of tumors because they have to do with the hormonal and/or metabolic abnormalities prevalent in obesity. Alternatively, they may be site specific, in which conditions can foster a particular tumor in a particular site because they have to do with the consequential effects of obesity, so leading to complications in specific tissues or organs [69].

Interestingly, human adipose tissue macrophages resemble human tumor-associated macrophages and increase the expression of FAS in cancer cells, thus playing a critical role in cancer cell survival [70]. Adiponectin and leptin have been subject to much study in cancer development as they are the most abundant adipokines. Higher leptin levels can be a factor for fostering cancer development and progression since it is now known to be mitogenic, proinflammatory, antiapoptotic, and proangiogenic [71]. Adiponectin, being the most abundant adipokine, is particularly interesting because it enhances insulin sensitivity, and its circulating levels are inversely related to cancer occurrence and cancer stage [72].

Finally, the expanded adipose tissue in obese individuals constitutes an important initiator of the microenvironment favorable for tumor development [73] and noteworthy, novel adipokines (lipocalin-2 (LCN-2),osteopontin (OPN) and YKL40)related to inflammation and insulin resistance with emerging roles in tumor development have been recently described to be increased in adipose tissue from patients with colocancer [73].

Depression

Obesity notably increases the possibility of developing depression. Depressive people featuring impaired stimulus, lack of motivation, isolation, and they also have higher incidence of obesity-related complications. Periabdominal fat is a better predictor of depression and anxiety than whole body adipose mass. Current evidence suggests that metabolic abnormalities related with central obesity and metabolic disease could also be responsible for the higher incidence of depression in obesity [74].

Depressed mood not only diminishes and impairs quality of life and functioning, but also features additional threats to obese individuals due to the variability in adherence to treatment, lifestyle changes and increasing the risk of complications related with adiposity. Abdominal fat and poor diet quality have been directly correlated with the development of depression during obesity [75-79]. In addition, there is also a bidirectional circuit linking obesity and depression in which depressed subjects gain excessive weight in o a mayor extent due to poor food choices and sedentarism [74-76].

Psicologycal disorders such as anxiety and depression can also affect food choice, energy metabolism and expenditure. Subjects with depressive disorders prefer palatable "comfort foods" and they self-report the consumption of these foods to alleviate, at least partly, negative feelings related with depressive mood [77]. It has been also reported that short-term consumption of palatable "comfort foods" can provide relief from negative feelings and mood states, while chronic consumption of hich caloric foods and subsequent increases in body fat mass could increase vulnerability to depression and anxiety [77-80]. In addition, recently it has been reported that animal models consuming a saturated high-fat diet for 12 weeks show depressive-like features such as immobility in the forced swim and reduced exploratory behavior [80].

Infectious diseases

Growing evidence reveal a link between obesity and infectious diseases [81]. Although the potential mechanisms underlying these findings are not well elucidated, a high number of potential factors could be involved [82]. Obesity can influence the risk of getting an infection and its outcome once it is established. Immune system dysregulation related with obesity, decrease cellular immune responses, comorbidities and respiratory dysfunction. Pharmacological issues have been proposed as underlying mechanisms [81,82]. However, in spite of the importance of the issue, not enough scientific evidence, no dosing guidelines of antimicrobials for obesity have been published, although such would be eagerly awaited [83].

Obesity has major effects on immune surveillance [84]. Immune cells and adipocytes have hystologycal and functional similarities such as the production of several inflammatory cytokines [84,85]. Adipose tissue mediates immune system and adipocytes interactions by the secretion of adipokines, such as leptin [85]. Macrophages differetiation is affected by obesity and complex interactions take place between immune cells and metabolic cells. Obesity impairs the balanced interaction of adipocytes and immune cells, disturbing the immune surveillance system. This leads to dysregulated immune response, uneffective chemotaxis and impaired macrophage differentiation [84,85].

Reports about the interactions between obesity and infection have increased by the influenza H1N1 pandemic, showing that obesity affects the disease course, increasing the mortality rate [86]. A recent retrospective case–control study showed obesity as an independent predictor of nosocomial infection in older subjects [87]. Morbid obesity and obesity combined with insulin resistance are considered as risk factors for periprosthetic infection after arthroplasty [88]. Obesity is also considered a risk factor for gallstones, gallbladder disease and pancreatitis.In addition, causes changes in skin barrier function, the lymph system, collagen structure and function, and wound healing. Obesity is also associated with a wide range of dermatological disorders [89]. Cohort studies have shown the link between obesity and increased risk of hepatic steatosis and fibrosis in patients with chronic hepatitis C infection [86,90,91].

Oral health

Recent studies have suggested that obesity is associated with

oral diseases, particularly chronic periodontitis [92-94]. It has been reported that obesity is second (just after smoking) as the strongest risk factor for inflammatory periodontal tissue disease [95]. In several studies, measures of abdominal obesity such as high waist circumference and waist-to-hip ratio appeared to be more strongly related than overall obesity (BMI) to higher periodontal disease prevalence [96,97,98]. The adipose tissue actively secretes a variety of cytokines and hormones that are involved in inflammatory processes, pointing towards similar pathways involved in the pathophysiology of obesity, chronic periodontitis and related inflammatory diseases [99].

Increased cytokines, such as TNF-α, IL-6, and acute-phase respondents such as CRP [100], contribute to the development of a low-grade systemic inflammation and may enhance periodontal tissue destruction [101]. In addition, enhanced TNF-α level may lead to an increase in PAI-1 levels for obese individuals [102] and in periodontitis, elevated levels of PAI-1 activity are observed compared with healthy controls. This may increase the potential for impaire fibrinolysis, a condition that results in a prothrombotic state [103]. Conversely, several studies have provided evidence that PAI-1 plays an important role in the process of gingival inflammation and destruction of periodontal connective tissue via decreased blood flow in periodontal tissues [104-106].

Approach to Obesity Prevention

Diet

Diet and life style seem to be two major causes of obesity and are associated with increasing industrialization, urbanization, and mechanization [107]. An increasing number of studies now indicate that a substantial initial weight loss predicts a larger long-term net weight loss [108-110]. Meal replacements, rich in nutrients but low in caloric content, work both directly and indirectly to reduce energy intake. Because many obese patients underestimate energy intake [111], meal replacements can be effective at reducing food choices and therefore facilitate a balanced energy intake. High-protein diets (20–30 % of energy) have been shown to increase satiety, preserve fat-free mass, and sustain energy expenditure via diet induced thermogenesis [112]. Low-glycemic-index foods may also be beneficial in weight control by increasing satiety and possibly by promoting fat oxidation at the expense of carbohydrate oxidation [113].

ω-3 fatty acids

Increasing evidence has shown that high-fat diet, in particular, enriched in saturated fat while lacking appropriate portion of unsaturated fat, may directly facilitate the prevalence of obesity worldwide. However, it is the amount and composition of dietary fat, but not the fat per se, that accounts for obesity. Numerous studies have suggested that specific fatty acids can influence body adiposity [107].

Although obesity is a disorder of energy homeostasis, understanding of its causes and treatment still remains unclear. There is controversy about the beneficial effects of supplementation with LC ω-3 PUFA on reducing body fat mass. Some studies report a positive correlation of ω-3PUFA consumption and weight loss [114] and decreased adipose tissue mass [115], whereas other studies have shown no effect of these fatty acids on adiposity [116]. In addition, it has also been suggested that ω-3 plasma levels are significantly reduced in obese subjects compared to normal non obese subjects, suggesting that high concentrations of ω-3 inhibit the expansion of adipose tissue or even reduces weight. In this respect, there is a reccomendation to increase ω-3 levels prior to begin a low-energy diet to get a greater weight reduction [117].

The mechanisms underlying LC ω-3 PUFA effect in the reduction of body fat and/or body weight are still unclear. One of the mechanism proposed suggest that ω-3 modulates lipid metabolism promoting lipolysis and liver fatty acid β-oxidation, inhibiting fatty acid synthesis and very low density lipoprotein (VLDL) secretion. DHA plays a key role in hepatic lipid synthesis, having a major impact on hepatic lipid metabolism and is involved in the inhibition of lipogenesis ([118]. The reduction in visceral adiposity has been associated with a decrease in adipocyte size [119] and a reduction in the number of adipocytes [120].

Increasing ω-3 intake during the growth years instead of dietary supplementation with large doses over a short duration in adults influences body fat mass. In this sense, it has been reported a higher concentration of ω-3 plasma levels in normal weight subjects compared to overweight individuals, however duration of intake of ω-3 remains unclear [121]. ω-3 LC-PUFA incorporates into the adipose tissue to influence weight and, despite long-term supplementation in adults, an increase in the levels of EPA and DHA in adipose tissue is modest [122]. Late foetal and early postnatal life is a highly sensitive period in which adipose tissue suffer a fast expansion [123], fact that could be a critical opportunity to improve the balance of fatty acids involved in adipogenesis and lipogenesis. Studies of maternal supplementation in which mothers received a DHA supplement from 21 weeks gestation until the the third month of lactation, reported a significant effect of DHA on weight gain and body mass index (BMI) reduction in their neonates at 21 [124]. Thus, at the light of these considerations, the role of ω-3 for weight management, require further considerations.

Water consumption

Drinking a lot of water is publically believed to support weightloss efforts or maintenance and has become a commonly used practice for weight control [125]. The advice to drink plenty of water has also been proposed in several popular weight-loss diets [126]. In fact, drinking plenty of water is a widespread weight-loss approach; according to NHANES data, 30% of all adults who tried to lose weight stated that they drank a lot of water [127]. It has been proposed that the increasing prevalence of obesity may be connected with the shift from the consumption of water to sugarcontaining beverages such as soft drinks and fruit juices [128,129]. Because tap water is widely and economically accessible, a recommendation of increased water consumption to prevent overweight and obesity may become relevant for public health. Especially in countries where drinking water from the tap is safe and palatable, tap water should be promoted as the preferred water source. In countries where tap water is still potentially contaminated, the provision of safe tap water should have priority [130].

Exercise

Regular exercise training has meaningful health benefits for individuals of any weight. These guidelines suggest that individuals should strive to achieve at least 150 minutes per week of moderate-

intensity physical activity combined with at least 2 days per week of resiatance training activity. However, for those who prefer to participate in vigorous-intensity physical activity, the minimal weekly goal is only 75 minutes or more per week. There is sufficient evidence to conclude that exercise training interventions, in the absence of dietary intervention, produce only modest weight loss [131].

In a study that compared the relative contribution of exercise training versus that of weight loss, overweight and obese subjects with insulin resistance were randomized to either diet-induced weight loss, or diet-induced weight loss combined with exercise training [132]. Both groups experienced comparable degrees of total body weight loss, fat mass loss, and comparable improvements in skeletal muscle insulin sensitivity. However, only the group that combined training with caloric restriction experienced an improvement in mitochondrial content and respiratory chain enzymatic activity, demonstrating that exercise training, not weight loss, is the key factor responsible for mitochondrial plasticity. Subsequent studies have confirmed that exercise training can increase SkM mitochondrial content in insulin-resistant subjects with and without type-2 DM [133,134].

Conclusion

Since a high number of non-pharmacological interventions are discussed, pharmacological interventions are not within the scope of this review. Obesity is a condition in which excess body fat has accumulated to the extent that it has an adverse effect on a person's physical, mental and/or social health. The global prevalence of obesity increased substantially in the past four decades regardless of age, gender, race, and ethnicity. Unlike other pandemics, however, obesity does not cause disease directly but instead functions as a potent independent risk factor for a number of chronic pathologies, including type-2 DM, CVD, neurodegenerative disorders, and cancer, inducing immense harm in both health and economic terms. The adverse metabolic changes associated with insulin resistance occur as a result of inflamed adipose tissue and ROS generation. The obesity-induced inflammation and subsequent insulin resistance may be a key pathogenic link between immunology and metabolism. Parallel to the increase of this disease, the study of obesity has undergone considerable development.

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Ann Nutr Disord & Ther - Volume 1 Issue 2 - 2014
ISSN : 2381-8891 | www.austinpublishinggroup.com

Citation: Díaz-Castro J, Hijano S, Pulido-Morán M, Kajarabille N, Ochoa JJ. Obesity: A Brief Approach to this New Pandemia. Ann Nutr Disord & Ther. 2014;1(2): 1010.